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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,603	CHAPPEY ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,13,21,24,25,29,31 and 39-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,13,21,24,25,29,31 and 39-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/6/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 06 July 2010.

Claims 2-11, 14-20, 22, 23, 26-28, 30 and 32-38 have been cancelled.

Claims 1, 42, 43 and 60 have been amended.

Claims 1, 12, 13, 21, 24, 25, 29, 31 and 39-60 are pending and currently examined.

Claim Objections

The objection to claim 1, 42 and 60 is withdrawn in response to Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(New Rejection) Claims 1, 12, 13, 21, 24, 25, 29, 31 and 39-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

These claims are drawn to methods comprising investigating a genus of mutations at position 11, 47, 50, 76, 83, 91 or 95 and 32, 33, 43, 46, 48, 54, 58, 71, 79, 82 or 84 of the protease protein sequence of a HIV-1 strain. This method requires that the amino acid mutations have the indicated activity of eliciting resistance to the protease inhibitor, amprenavir. The specification indicates that the wild type residue at this position is compared to a reference strain NL4-3 of HIV-1. This genus includes mutations to any residue that is different from the wild type residue, except for I47V, I50V, V32I, M46I, M46L, I54L, I54M, I84V or 79P. Thus, the claims are drawn to methods of using any amino acid change at the aforementioned position of the HIV-1 protease sequence, which have an indicated function.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice .... reduction to drawings .... or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In support of the claimed invention, the application discloses only one or, at the most, three mutation species for each of position 11, 47, 50, 76, 83, 91, 95, 33, 43, 46, 48, 54, 58, 71, 79, 82 or 84. See paragraph [0085] and [0097]. However, the application does not disclose any other of such mutation residues as being associated with the amino acid mutation's function (eliciting amprenavir-resistance activity) or identify any shared structure or motif correlating with the function. It is further noted that, while the application may have provided means by which such mutants could be identified, such does not provide descriptive support for the proteins which may eventually be identified through performance of the methods. See *e.g.*, *University of Rochester v G.D. Searle & Co.*, 69 U.S.P.Q.2d 1886, at 1895 (CAFC 2001). Thus, the application provides little information with respect to the identity of mutation residues at the above positions in the HIV-1 protease sequence which retain the required activity.

It is known in the art that the effects of amino acid substitution in a protein are unpredictable. See e.g., Bowie *et al.*, Science 248: 1306-10, esp. page 1306 (teaching that while proteins are generally tolerant of amino acid substitutions, depending on the relationship of a particular residue to protein function and/or structure, a particular residue position may be extremely tolerant, may allow only conservative changes, or may not permit any substitutions). Thus, while the art indicates that it is likely that there are many mutants of the disclosed protein that would retain the activity, in the absence of the identification of the residues and structures associated with the required activity, there is significant uncertainty as to which such mutant residues would have the required functions. Especially when an isoleucine is changed to leucine or when a valine is changed to alanine, which has a structurally similar side chain of the same charge, it is highly unpredictable whether such a mutation would affect the protease inhibitor binding site in the HIV-1 protease and thereby elicit resistance or reduce amprenavir susceptibility. For example, Colonno *et al.* (2004, J. Infect. Dis. 189:1802-10) teach that a substitution of two different amino acids at the same amino acid position does not result in similar resistance properties. Colonno *et al.* teach that a substitution of leucine for isoleucine at position 50 of the protease gene reduces susceptibility to one protease inhibitor (i.e., atazanavir), and increases susceptibility to another protease inhibitor (i.e., amprenavir) (page 1808, Table 4). In addition, a different amino acid substitution at the same position has a different effect. A substitution of valine instead at position 50 actually confers reduced susceptibilty to amprenavir and increased susceptibility to atazanavir. Therefore, Colono *et al.* clearly

teach that a single amino acid substitution can have dramatically different effects with respect to two different protease inhibitors. Colono *et al.* also teach that two different amino acid substitutions at the same amino acid position can have very different impacts on protease inhibitor susceptibility.

In view of the limited descriptive support provided for recited mutations, the lack of a number of provided examples of such mutations retaining the required function, and the uncertainty in the art regarding the modification of such amino acid residues such that the required function is maintained, the claims are rejected for lacking adequate descriptive support for the entire scope of the genus of mutations at the HIV-1 protease positions as recited in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Prior Rejection – Withdrawn) The rejection of claims 1, 12, 13, 21, 24, 25, 29, 31 and 39-60 under 35 U.S.C. §102(b) as being anticipated by Carrillo *et al.* (1998, No. B17 in IDS filed on 17 February 2006) is **withdrawn** in response to Applicant's amendment adding a new limitation of the active method step of determining whether the HIV-1 has an increased likelihood of having a reduced susceptibility to treatment with amprenavir.

Response to Arguments

Applicant's arguments with respect to claims 1, 12, 13, 21, 24, 25, 29, 31 and 39-60 have been considered but are moot in view of the following new ground of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(New Rejection) Claims 1, 12, 13, 21, 24, 25, 29, 31 and 39-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrillo *et al.* (1998, No. B17 in IDS filed on 17 February 2006, hereinafter "Carrillo") in view of Gilden (1999).

Claim 1 is directed to a method comprising: detecting the presence of one mutation at position 11, 34, 47, 50, 76, 83, 91 or 95 of an amino acid sequence of a HIV-1 protease, with the proviso that said mutation is not I47V or I50V, and wherein the level of susceptibility, mutations, and position number are compared to the protease sequence of the NL4-3 reference strain; and determining whether the HIV-1 has an increased likelihood of having a reduced susceptibility to treatment with amprenavir,

Claim 42 further limits claim 1 to detect multiple mutations in at least 2, 3, 4, 5, 6, 7, or 8 of the positions. Claim 43 further limits claim 1 to additionally detecting at least one mutation at amino acid 32, 33, 43, 46, 48, 54, 58, 71, 79, 82 or 84, with the proviso

that the mutation is not V32I, M46I, M46L, I54L, I54M, or I84V. Claim 60 further limits claim 43 to detect multiple mutations in at least from 2 to 19 of the positions.

Carrillo discloses detection of mutations in the protease gene of HIV-1 strain NL4-3 after treatment with a protease inhibitor, ABT-378 (page 7532, right column, lines 12-16 of the full paragraph). By sequence analysis of the protease coding region from HIV-1 passaged with the ABT-378 or Lopinavir, the following claimed mutations are identified: L33I, E34A, E34K, A71V, L76V, V82A and T91S (see page 7534, Figure 2) when compared with the protease sequence of wild-type NL4-3 strain.

Although Carrillo discloses an increase in the likelihood of having a reduced susceptibility to treatment with a different protease inhibitor, ABT-378, Carrillo does not disclose the above mutations being associated with an increase in the likelihood of having a reduced susceptibility to treatment with amprenavir.

Gilden discloses that the amprenavir-resistant mutations at protease codon 10, 46 and 54 commonly contribute to broad cross-resistance to protease inhibitors in multidrug-resistant HIV (see the third paragraph under the title "Amprenavir (Agenerase)") and further discloses that ABT-378's activity is hobbled by many of the same protease mutations that affect amprenavir (see the second paragraph under the title "ABT-378").

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Carrillo *et al.* so as to include a further step of determining the likelihood of the HIV-1 having a reduced susceptibility to treatment with amprenavir with a reasonable expectation of success because the prior art

suggests that the same mutations contribute to cross-resistance to both amprenavir and ABT-378, as disclosed by Gilden. One having ordinary skill in the art would have been motivated to make such a modification to further characterize the HIV-1 to complete its drug resistance profile and to provide better assessment of the effectiveness of each HIV inhibitor towards the specific HIV strain. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zac Lucas, can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648